Synthesis of Monoaryl Hydrazides via the BF$_3$ Catalyzed Reaction of Diethyl Azodicarboxylate with Substituted Benzenes

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Abstract DiethylAzodicarboxylate (DEAD) reacted readily with sufficiently activated aromatic compounds in the presence of 25 mol% BF$_3$•O(Et)$_2$ as Lewis acid catalyst to afford monoarylhydrazides in reasonable-to-high yields (41-94%).

Keywords Arenes, Azodicarboxylates, Electrophilic Aromatic Substitution

1. Introduction

Monoarylhydrazides (1, Scheme 1) are important intermediates for the synthesis of a variety of biologically active heterocycles including indoles[1], oxadiazolones[2], and pyrazolones[3]. Thus, it is not surprising that the pursuit of new and improved methods for the synthesis of aryl hydrazides remains an active area of research[4].

Scheme 1. Synthesis of MonoarylHydrazides via Electrophilic Aromatic Substitution of Azodicarboxylates

Many routes for the synthesis of monoarylhydrazides have been devised including metal-mediated coupling of unsubstitutedhydrazides to haloaromatics[5], Pd or Cu-catalyzed coupling of dialkylazodicarboxylates to aryboronic acids [4e,6], the addition of organometallic reagents to azodicarboxylates[7], and electrophilic aromatic substitution (EAS) of dialkylazodicarboxylates 2 onto aromatic rings (see Scheme 1)[8]. EAS reactions are a particularly economical synthetic method since most of the other methods rely upon access to haloaromatic starting materials that are typically formed from EAS reactionsthemseleves. Several methods have been reported for effecting EAS reactions of azodicarboxylates with aromatic rings[8]. However, they generally require strongly acidic conditions (e.g., mixtures of TfOH and CF$_3$CO$_2$H)[9], expensive metal catalysts (e.g., Sc(OTf)$_3$, InCl$_3$, AuCl$_3$) [4b,10], or the use of the highly electron-deficient (and expensive) bis(2,2,2-trichlorovinyl) azodicarboxylate[4b,9a,11]. The Lewis acid catalyst BF$_3$•O(Et)$_2$ is easy to work with and inexpensive. While there have been a few isolated reports of BF$_3$-catalyzed EAS reactions of readily available diethyl azodicarboxylate (DEAD, 2, where R = Et) with aromatic substrates[12], we could find no studies that investigated the scope or limitations of the reaction. The results of our preliminary investigations on these reactions are presented here.

2. Results and Discussion

In the few studies that reported the use of the Lewis acid BF$_3$ to catalyze the EAS reactions of DEAD with aromatic compounds, one or more equivalents of the acid catalyst were utilized[12]. Indeed, the addition of one equivalent of BF$_3$•O(Et)$_2$ to an equimolar mixture of DEAD (2.5 mmol) and anisole in CH$_2$Cl$_2$ as solvent resulted in formation of the desired adduct 3a (Figure 1) in reasonable yield (64%). We were able to decrease the catalyst load to 25 mol% without affecting the product yield (64%) although the reaction required somewhat longer reaction time (1 h vs 0.5 h). In both cases, a substituted product was formed in addition to the desired monoadduct. This is not surprising given that the monoadducts were found to be electronically activated relative to starting anisole. Using 2 equivalents of anisole was enough to virtually eliminate the formation of the disubstituted product and the yield of 3a increased to 90%. We subsequently found that with other substrates, such as 1,3-dimethoxybenzene to form 3c (vide infra), upwards of 10 equivalents of the aromatic substrate were required to...
squelch formation of di- and polysubstituted products. Fortunately, however, in these cases unreacted aromatic starting material could be readily recovered (after quenching of the BF₃ catalyst) via either direct distillation from the crude reaction mixture or column chromatography.

A variety of aromatic substrates were subjected to the same reaction conditions previously optimized for anisole (i.e., 0.25 equivalents of BF₃, 1-10 equivalents of aromatic substrate) to afford the expected monoadducts in good to excellent yields (Figure 1). 1,3,5-Trimethoxybenzene reacted similarly to anisole to form 3b in high yield. Curiously, however, the reaction of DEAD with two equivalents of 1,3-dimethoxybenzene afforded 3c in only 33% yield, the remainder of the product being disubstituted. Employing 5 equivalents of 1,3-dimethoxybenzene increased the yield to 59%, but formation of the disubstituted product persisted. We wondered whether in this case the BF₃ catalyst was prone to complexation with monoadduct 3c and acted to direct further substitution onto the complexed ring, thus accounting for the unusual preference for disubstitution. We tested this theory by adding DEAD to a premixed solution of 1,3-dimethoxybenzene (5 eq) and a full equivalent of BF₃ thereby maximizing the interaction of DEAD with non-complexed BF₃ and aromatic substrate. However, a yield nearly identical to the reaction conducted under standard conditions was observed (60%). Under the standard conditions, with 10 equivalents of substrate, 3c was formed in 72% yield.

A series of methylated arenes including pentamethyldibenzene, durene, mesitylene and m-xylene all afforded excellent yields of the expected hydrazide products 3d-g, respectively (Figure 1).

The reaction appears to be successful with aromatic compounds at least as electronically activated as toluene. For example, whereas m-xylene readily engaged in reaction at room temperature to afford 3g, reaction with toluene required heating to 60°C and employing toluene as solvent for the reaction. Even then, only a modest yield (42%) of adduct 3h was observed (although this compares favorably with the yield recently reported[38%] for the corresponding AuCl₃-catalyzed reaction of the highly electrophilic bis(2,2,2-trichloroethyl) azodicarboxylate with toluene)[4b]. Unfortunately, no reaction with benzene (as solvent) was observed even after heating the reaction mixture to 80°C. However, unsubstituted naphthalene afforded a reasonable yield (65%) of hydrazide 3i (Figure 1).

Finally, we have also begun testing the reactivity of other commercially available azodicarboxylates. In particular, diisopropylazodicarboxylate (2, where R = iPr) and di-tert-butyl azodicarboxylate (2, where R = tert-Bu) were subjected to the reaction conditions optimized for DEAD. Diisopropylazodicarboxylate reacted with anisole to afford hydrazide 4 in 90% yield (Figure 2)[12e]. Di-tert-butyl azodicarboxylate was found to be unstable to the reaction conditions and only black tarry product mixtures were obtained.

These initial studies have proven that BF₃•O(Et)₂ is an effective Lewis acid catalyst for promotion of the addition of DEAD to substituted benzenes. We are currently continuing to optimize the reaction conditions in terms of solvent effects and catalyst load. We are also extending the studies to more complex aromatic substrates. We will report on our complete findings in due course.

3. Experimental

3.1. General Procedure for the Reaction of Diethyl Azodicarboxylate (DEAD) with Substituted Benzenes

To a stirring solution of aromatic substrate (1-10 equivalents as per Figure 1) in 8 mL CH₂Cl₂ was added 0.44 g (2.5 mmol) of DEAD as a solution in 2 mL CH₂Cl₂.
followed by 80 µL (0.63 mmol, 25 mol%) of BF₃·(Et)₂O via syringe. The resulting solution stirred until the DEAD was completely consumed (as determined by TLC). The reaction mixture was washed with H₂O (10 mL), and the resulting organic layer dried over Na₂SO₄, filtered, and concentrated. The product was purified via column chromatography (SiO₂, using mixtures of EtOAc and hexanes as eluent).

3.1.1. Diethyl 1-(4-methoxyphenyl)hydrazine-1, 2-dicarboxylate (3a)

According to the general procedure using 0.54 g (5 mmol, 2 eq) of anisole, 0.70 g (2.26 mmol, 90% yield) of 3a was isolated as a colorless viscous oil.

1H NMR (60 MHz, CDCl₃): 7.92 (br s, 1H, NH), 7.35 (d, 2H, J = 9.2 Hz), 6.81 (d, 2H, J = 9.2 Hz), 4.19 (q, 2H, J = 7.1 Hz), 4.18 (q, 2H, J = 7.1 Hz), 3.74 (s, 3H), 1.22 (br t, 6H, J = 7.1 Hz).

13C NMR (14 MHz, CDCl₃): 156.5, 155.6, 138.0, 137.6, 135.2, 131.5, 127.4, 127.0, 62.5, 61.6, 20.9, 18.2, 14.5, 14.4.


According to the general procedure using 3.45 g (25 mmol, 10 eq) of m-xylene, 0.62 g (2.21 mmol, 89% yield) of 3g was isolated as a colorless viscous oil; mp 83-84 °C (lit.[12d] 81-82 °C).

1H NMR (60 MHz, CDCl₃): 7.4-6.9 (m, 4H), 4.15 (q, 2H, J = 7.1 Hz), 3.13 (q, 2H, J = 7.1 Hz), 2.31 (s, 3H), 2.26 (s, 3H), 1.23 (t, 3H, J = 7.1 Hz), 1.18 (t, 3H, J = 7.1 Hz).

13C NMR (14 MHz, CDCl₃): 156.3 (2C), 138.9, 134.6, 132.1, 131.5, 62.8, 61.9, 20.0, 14.7, 14.6, 14.4.

3.1.4. Diethyl 1-(2,3,4,5,6-pentamethylphenyl)hydrazine-1, 2-dicarboxylate (3d)

According to the general procedure using 0.37 g (2.5 mmol, 1 eq) of 1,2,3,4,5-pentamethylbenzene, 0.73 g (2.27 mmol, 91% yield) of 3d was isolated as a white solid; mp 179-181 °C.

1H NMR (60 MHz, CDCl₃): 6.96 and 6.81 (br s, 1H, NH), 4.21 (q, 2H, J = 7.1 Hz), 4.17 (q, 2H, J = 7.1 Hz), 2.26 (s, 6H), 2.20 (s, 9H), 1.25 (t, 3H, J = 7.1 Hz), 1.20 (t, 3H, J = 7.1 Hz).

13C NMR (14 MHz, CDCl₃): 156.5, 156.2, 136.9, 135.4, 133.5, 131.7, 62.8, 61.9, 16.9, 16.7, 15.7, 17.7, 14.4.

Anal. Calcd. For C₁₇H₂₆N₂O₄: C, 63.32; H, 8.13; N 8.69. Found: C, 63.24; H, 8.36; N, 8.62.

3.1.5. Diethyl 1-(2,3,5,6-tetramethylphenyl)hydrazine-1, 2-dicarboxylate (3e)

According to the general procedure using 1.68 g (12.5 mmol, 5 eq) of durene, 0.65 g (2.11 mmol, 85% yield) of 3e was isolated as a white solid; mp 185-186 °C.

1H NMR (400 MHz, CDCl₃): 7.32 (br s, 1H, NH), 6.96 (br s, 1H) 4.20 (q, 2H, J = 7.1 Hz), 4.16 (q, 2H, J = 7.1 Hz), 2.22 (s, 12H), 1.23 (t, 3H, J = 7.1 Hz), 1.19 (t, 3H, J = 7.1 Hz).

13C NMR (14 MHz, CDCl₃): 156.3(2C), 138.9, 134.6, 132.1, 131.5, 62.8, 61.9, 20.0, 14.7, 14.6, 14.4.

3.1.6. Diethyl 1-(2,4,6-trimethylphenyl)hydrazine-1, 2-dicarboxylate (3f)

According to the general procedure using 1.50 g (12.5 mmol, 5 eq) of mesitylene, 0.69 g (2.35 mmol, 94% yield) of 3f was isolated as a white solid; mp 159-160 °C (lit.[12c] 159-161 °C).

1H NMR (60 MHz, CDCl₃): 7.52 and 7.23 (br s, 1H, NH), 6.87 (br s, 2H), 4.14 (q, 2H, J = 7.1 Hz), 4.10 (q, 2H, J = 7.1 Hz), 2.34 (s, 6H), 2.26 (s, 3H), 1.22 (t, 3H, J = 7.1 Hz), 1.18 (t, 3H, J = 7.1 Hz).

13C NMR (14 MHz, CDCl₃): 156.47 (2C), 138.9, 137.6, 135.2, 131.1, 62.9, 61.9, 20.9, 18.3, 14.2 (2C).

3.1.7. Diethyl 1-(2,4-dimethylphenyl)hydrazine-1, 2-dicarboxylate (3g)

According to the general procedure using 0.43 g (25 mmol, 10 eq) of m-xylene, 0.62 g (2.21 mmol, 89% yield) of 3g was isolated as a white solid; mp 83-84 °C (lit.[12d] 81-82 °C).

1H NMR (60 MHz, CDCl₃): 7.4-6.9 (m, 4H), 4.15 (q, 2H, J = 7.1 Hz), 3.13 (q, 2H, J = 7.1 Hz), 2.31 (s, 3H), 2.26 (s, 3H), 1.25 (t, 3H, J = 7.1 Hz), 1.22 (t, 3H, J = 7.1 Hz).

13C NMR (14 MHz, CDCl₃): 156.5, 155.7, 138.0, 137.6, 135.2, 131.1, 127.4, 127.0, 62.5, 61.6, 20.7, 17.3, 14.2(2C).

3.1.8. Diethyl 1-(4-methylphenyl)hydrazine-1, 2-dicarboxylate (3h)

According to the general procedure using 10 mL of toluene as solvent and heating the reaction mixture to 60 °C for 24 h, 0.28 g (1.05 mmol, 42% yield) of 3h was isolated as a colorless viscous oil.

1H NMR (60 MHz, CDCl₃): δ (mixture of isomers) 7.8 and 7.66 (br s, 1H, NH), 7.39-7.00 (m, 4H), 4.15 (q, 2H, J = 7.1 Hz), 4.12 (q, 2H, J = 7.1 Hz), 2.30 (s, 3H), 1.23 (t, 6H, J = 7.1 Hz), 1.18 (t, 3H, J = 7.1 Hz).
Hz).  
$^1$H NMR of para isomer (14 MHz, CDCl$_3$): $\delta$ 156.6 (2C), 139.3, 136.2, 129.2, 124.4, 62.8, 62.1, 20.9, 14.4 (2C).

$^1$C NMR of ortho isomer (14 MHz, CDCl$_3$): $\delta$ 155.2 (2C), 140.4, 135.6, 130.7, 128.2, 127.7, 126.6, 62.8, 62.1, 17.7, 14.4 (2C).

HRMS (EI) $m/z$ [M+Na]$^+$ calculated for C$_{13}$H$_{18}$N$_2$NaO$_4$: 289.1159. Found 289.1160.

3.1.9. Diethyl 1-(naphthalen-2-yl)hydrazine-1, 2-dicarboxylate (3i)

According to the general procedure using 1.60 g (12.5 mmol, 5 eq) of naphthalene, 0.49 g (1.63 mmol, 65% yield) of 3i was isolated as a white solid; 137 - 138 °C[10].

$^1$H NMR (60 MHz, CDCl$_3$): $\delta$ 8.07-7.26 (m, 8H), 4.15 (q, 4H, $J = 7.1$ Hz), 1.25 (t, 3H, $J = 7.1$ Hz), 1.13 (br t, 3H, $J = 7.1$ Hz).

$^1$C NMR (14 MHz, CDCl$_3$): $\delta$ 156.7, 156.1, 138.0, 134.5, 130.2, 128.9, 128.4, 126.9, 126.3, 126.0, 125.7, 122.8, 63.1, 62.2, 14.5 (2C).

Anal. Calc'd. For C$_{16}$H$_{18}$N$_2$O$_4$: C, 63.55; H, 6.00; N, 9.27. Found: C, 63.71; H, 6.25; N, 9.19.

3.1.10. Diisopropyl 1-(4-methoxyphenyl)hydrazine-1, 2-dicarboxylate (4)

According to the general procedure using 0.54 g (5 mmol, 2 eq) of anisole and 0.51 g (2.5 mmol) of diisopropyl azodicarboxylate, 0.70 g (2.26 mmol, 90% yield) of 4 was isolated as a colorless viscous oil. Spectral data were in accord with literature values[4c,e].

4. Conclusions

In summary, the reaction of DEAD with sufficiently activated aromatic compounds provides a general, high-yield method for the synthesis of monoarylhydrazides. The optimized method requires only 25 mol% of the inexpensive and readily available Lewis acid catalyst BF$_3$•O(Et)$_2$. The greatest limitation is the requirement for aromatic rings at least as electronically activated as toluene.

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